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EXAMINER
NOBLE, MARCIA STEPHENS

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/619,055	ECHELARD ET AL.	
	Examiner	Art Unit	
	Marcia S. Noble	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *19 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,14,17 and 22-24* is/are pending in the application.

4a) Of the above claim(s) *12,13,15,16,18-21 and 25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,14,17 and 22-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/13/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of group I, claims 1-11, 14, 17, and 22-24 in the reply filed on 12/19/2005 is acknowledged. Cancellation of claims 12, 13, 15, 16, 18, 19, 20, 21, and 25 as pertaining to other subject matter is acknowledged. Amendments to the specification and claims to correct grammatical errors are also acknowledged.

Specification

2. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered. References are listed on p. 19-20. Removal of these references and submitting them via PTO-892 for consideration would be remedial.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140

F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 1-4, 6-11, 14, 17, and 22-24 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-21, 23-25 of copending Application No. 11/081945. Although the conflicting claims are not identical, they are not patentably distinct from each other because they encompass the same scope.

The instant invention is drawn to a method of producing a transgenic animal comprising: transfecting a cell with a construct encoding a desired gene, selecting cells that have integrated the transgene into its genome, performing a first nuclear transfer with cell containing the transgene and producing a heterozygous transgenic animal, characterizing the genetic composition of said first transgenic animals, selecting cells homozygous for the transgene using a selective agent, characterizing surviving cells, and performing a second nuclear transfer to produce a second homozygous transgenic animal.

The claims from the copending application is drawn to a method of producing transgenic animals comprising: transfecting a prescreened cell with a construct

encoding a desired gene, selecting cells that have integrated the transgene into its genome, performing a first nuclear transfer with cell containing the transgene and producing a heterozygous transgenic animal, characterizing the genetic composition of said first transgenic animals. The majority of the claims are identical to those of the instant invention for the exception of claims 1, 4 and 16. Claim 1 of the copending application eliminates the steps of selecting cells homozygous for the transgene using a selective agent, characterizing surviving cells, and performing a second nuclear transfer to produce a second homozygous transgenic animal. Eliminating these steps effectively changes the scope of the copending application, but claim 16 restores the equivalent scope between the copending application and the instant invention because it claims a method of 1 that the transgenic prescreened cells lines selected can proceed to be used through a second of more rounds of selection to generate a homozygous transgenic cell line. Claim 4 of the copending application is essentially identical to that of claim 4 in the instant application except it specifies "pre-screened cells".

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-11, 14, 17, and 22-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue".

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The instant invention is drawn to a method of producing a transgenic animal comprising: transfecting a non-human mammalian cell line with a transgene construct

encoding a desired gene, selecting cell lines that have integrated the transgene into its genome, performing a first nuclear transfer to generate a first transgenic animal with desired gene, characterizing the genetic composition of said first transgenic animals, selecting cells homozygous for the transgene using a selective agent, characterizing surviving cells, and performing a second nuclear transfer with the surviving cells to produce a second homozygous transgenic animal.

The steps of transfecting a cell line with a construct encoding a desired gene and selecting cell lines that have integrated the transgene into its genome are not enabled in themselves. At present, the state of the art is that transgenic animals cannot be produced by transfecting cell lines. Currently, transgenic animals can only be produced from transfecting primary, diploid cell (Zakhartchenko et al. Mol Reprod Dev 54:264-272, 1999. p.268, col 2, par 1 of Discussion, lines 4-15). Zakhartchenko et al. demonstrate successful nuclear transfer in primary mammary fibroblast but failure to sucessfully do nuclear transfer in MECL mammary cell line using the same method. The differences may be due to chromosomal differences that prevent reprogramming. Furthermore, cell lines are many times polyploidy or aneuploidy and are not effectively been used to produce transgenic animals. Given the art does not provide a method of transfecting a cell line with a construct encoding a desired gene and selecting cell lines that have integrated the transgene into its genome, an artisan would be reliant upon the specification for guidance to use or made the instant invention. No guidance or working examples as to how an artisan would transfect a cell line with a construct encoding a

desired gene and selecting cell lines that have integrated the transgene into its genome, therefore an artisan would not know how to make or use the instant invention.

Although great advances have occurred in transgenic technology, the state of the art of generating transgenic animals is such that the resulting phenotype would not be predictable. This is because the art of transgenic animals has for many years stated that the unpredictability lies with the site or sites of integration of the transgene into the target genome. Transgenic animals are regarded to have within their cells cellular mechanisms which prevent expression of the transgene, such that DNA methylation or deletion from the genome (Kappell et al Current Opinions in Biotechnology 3, p. 549, col 2, par 2, 1992). Mullins et al states that not all animals express a transgene sufficiently to provide a model for a disease as the integration of a transgene into different species of animal has been reported to give divergent phenotypes (Mullins et al Hypertension 22:631, col 1, par 1, lines 14-17, 1993). The elements of the particular construct used to make transgenic animals are held to be critical, and that they must be designed case by case without general rules to obtain good expression (e.g. specific promoters, presence or absence of introns, etc. (Houdebine J. Biotech 34:281, 1994). "The position effect" and unidentified control elements also are recognized to cause aberrant expression (Wall. Theriogenology 45:61, par 2, lie 9 to p. 62, line 3, 1996.) Mullins et al disclose that "the use of non-murine species for transgenesis will continue to reflect the suitability of a particular species for the specific questions being addressed, bearing in mind that a given construct may react very differently from one species to the another." (Mullins et al. J Clin Invest 98:S39 summary, 1996) Well-

regulated transgene expression is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues (Cameron Mol Biotech 7:256, col 1-2, bridging par, 1997). Factors influencing low expression, or lack their of, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct (Cameron Mol Biotech 7:256, lines 3-9). These factors, thus, are copy number independent and integration site dependent, emphasizing the role the integration site plays on expression of the transgene (Cameron Mol Biotech 7:256, lines 10-13). Furthermore, Sigmund states that the random nature of transgene insertion, resulting founder mice can contain the transgene at a different chromosomal sire, and that the position of the transgene effects expression, and thus the observed phenotype (Sigmund Arteroscler Throm Vasc Biol 20:1426, col 1, par 1, lines 1-7, 2000). With reguard to the importance of promoter selection, Niemann states that transgenic pigs made with different promoters regulating expression of growth hormone gene give disparate phenotypes, one deleterious to the pig, the compatible with pig health (Neimann Trans Res 7:73, col 2, par 2, line 12 to p. 73, col 1, line 4, 1998). While the intent id not to say transgenic animals of a particular phenotype can never be made, the intent is to provide art taught reasoning as to why the instant claims are not enabled. Given such species differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for any transgenic non-human animal, it would have required undue experimentation to the levels of the transgene product, the consequences of that product, and therefore, the resulting phenotype. The specification fails to provide teachings or specific guidance to

overcome the above described unpredictabilities, in order to sucessfully carry out the claimed methods of nuclear transfer to produce a transgenic with a specific phenotype, and as such, the claims are not enabled.

The step of performing a first nuclear transfer to generate a first transgenic animal with desired gene is also not enabled because nuclear transfer is an unpredictable art. The specification provides general guidelines for nuclear transfer and some specifics as they pertain to goats, yet the breath of the claims is to all animals. The specification does not provide species specific information necessary for successful nuclear transfer. Westhusin et al. (Theriogenology, 55:35-49, 2001) review the state of the art of cloning. They state that, "Without a doubt, one of the major factors influencing the probability of cloning a specific animal is species. While the basic approach involving nuclear transfer may be similar, the specific materials and methods utilized for cloning one species of animal do not automatically apply across different species." (see p. 36 par 4) Westhusin et al further state that the factors to consider when cloning animals by nuclear transfer include acquisition of mature ova, enucleation of mature ova, nuclear transfer into the enucleated ova, activation of the reconstructed embryo, culturing the embryo in vitro and transferring the embryo into a recipient. Furthermore, these techniques and the efficiency of these techniques will vary form species to species (par bridging p 36 and 37). Westhusin et al. clearly teach the unpredictable state of the art of nuclear transfer with regard to the unpredictable factors such as species differences, donor cells and genetic modifications. Given the state of the art is unpredictable, an artisan would rely upon the specification to provide guidance to use or

make the instant invention. Since the specification only provides broad method of nuclear transfer and no details needed for successful nuclear transfer in any given species, an artisan would not be able to use or make the instant invention without undue experimentation.

An added measure of unpredictability is when combining transgenic techniques with nuclear transfer. Finding from Zakhartchenko et al. (Mol Repord Dev 60:362-369, 2001. see abstract) demonstrate that extended culture associated with transfection and selection associated with transgenesis may change donor cells which markedly decrease the efficiency of nuclear transfer and these changes are not reversed by recloning. Bordignon et al (Bio Reprod 68:2013-2023, 2003 see abstract) similarly saw that expression levels varied both between tissues and cells with the same tissue of cloned GFP transgenic calves, indicating a partial shutdown of GFP expression. Also, non-expressing fibroblast derived from transgenic offspring were unable to direct GFP expression after nuclear transfer and development to blastocysts, suggesting irreversible silencing of the transgene. Given this added level of unpredictability in the art and given that the specification does not address such complications, it is uncertain that an artisan could use or make the instant invention.

The method also includes selecting cells homozygous for the transgene using a selective agent and characterizing surviving cells. As the claim is written nothing links the steps of producing the transgenic cell line and first transgenic animal to these steps. Therefore as written, the above steps encompass obtaining any homozygous cell with the desired transgene, but the specification does not support this use. Also this part of

the claim is discussing cells when the other steps were drawn to cells lines. Given this lack of clarity and the implications of using cell over cell lines, an artisan would not be clear in the method being used and therefore would not be able to make or use the instant invention.

Furthermore, the specification disclosed in more detail that the selection is meant to be by utilizing a selectable marker and elevated does of a selective agent to select for the homozygote. This is not represent in the claims as such and provides for a gap in the method. The specification does not provide for a specific selection method that sucessfully discriminates between cells that are heterozygous and homozygous for a transgene. Mortensen et al. (of record) discloses method utilizing high doses of G418 to select for homozygous transgenic ES cell having a neomycin resistance gene as a selectable marker (see abstract), but these cells were not used for nuclear transfer and given unpredictable nature that transgenic selection may have on the outcome of nuclear transfer (Bordignon et al abstract) it is unclear that this method could reliably be used to select for homozygous transgenic cell for nuclear transfer.

Furthermore, the selecting of cells or cell lines for transgene integration alone has been shown to be unpredictable. Chen et al (Biol Reprod 67:1488-1449, 2002) teach < the advantage of using NT to produce transgenic animal is the ability to use pre-selected genetically modifies cells as donor nuclei. All of the animals created via NT from such selected cells should be but are not always transgenic. Several researchers...have observed the so-called bystander effect, where transgenic cells, which express the antibiotic-resistant gene, provide protection to nearby non-transgenic

cells either by secretion of the gene product into the medium or by direct cell-to-cell contact. As the result of this by stander effect, many transected colonies are mixed and contain both transgenic and non-transgenic cells. Unpublished results form our lab and studies from other groups...have shown that NT animals produced by drug-selected genetically modified donor cells are not always transgenic." (p. 1488, paragraph bridging col 1 and 2.). Given that produces of screening for the presence of the transgene are unpredictable and selection for allelic state can be the same as suggested by the specification, it is uncertain that the selection procedure provide valid detection of the transgene's presence let alone, if it is homozygous or heterozygous for the transgene.

Given the unpredictability of screening procedures, nuclear transfer, transgenesis and the added uncertainties of combining the two methodologies in the art and given that the specification lack specific guidance, an artisan would not known how to use or make the instant invention without undue experimentation.

Because claims 2-11, 14, 17 and 22-24 are dependent on claim 1, they are also not enabled for the reasons discussed above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1, and 6-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6-9 recites the limitation "said donor" in line 1. There is insufficient antecedent basis for this limitation in the claim. This was further considered vague and indefinite because it is not clear if donor refers to first or second or both rounds of nuclear transfer.

6. Claims 1-11, 14, 17, and 22-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 4 recite “several known molecular biology methods”. The metes and bounds of “several known molecular biology methods” are relative in time of use the method as well as dependent on the artisan doing the methodology and therefore considered vague and indefinite. Because molecular biology methods rapidly change, known molecular biology techniques at the time of filing, today, and in the future, when the instant methods may be use, are all different. Furthermore, because molecular biology is a very broad field and practiced widely in many disciplines, some molecular biology techniques that are standard to one artisan may not be known to another artisan.

Because claims 2-11, 14, 17, and 22-24 are dependent on claim 1, they are also considered vague and indefinite and are also rejected under 112 2nd.

7. Claims 1 and 4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 recites "...without limitation FISH...". The meaning of this phrase is not discernable by examiner and must be clarified.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 4, 5-11, 14, 17, and 22-24 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 0042174 (of record).

The instant invention is drawn to a method of producing a transgenic animal comprising: transfecting a cell with a construct encoding a desired gene, selecting cells that have integrated the transgene into its genome, performing a first nuclear transfer with cell containing the transgene and producing a heterozygous transgenic animal, characterizing the genetic composition of said first transgenic animals, selecting cells homozygous for the transgene using a selective agent, characterizing surviving cells, and performing a second nuclear transfer to produce a second homozygous transgenic animal.

WO 0042174 discloses the production of transgenic or non-transgenic animals by two consecutive rounds of nuclear transfer. This application discloses that the process may be used to introduce genetic modification into resultant offspring by gene manipulation and selection of the cells to act as nuclear donors prior to embryo reconstruction. In addition the process is disclosed as doing genetic modification by introducing multiple genetic modifications concomitantly into the cultured cell population,

repeated rounds of transfection and selection of the cultured cell population, repeated rounds of transfection, selection, nuclear transfer and re-isolation of a cell population from the embryo, fetus, juvenile, or adult animal so formed, or any combination thereof (p. 1 lines 7-15). Due to the breadth of this disclosure as supported by the accompanying claims (1, 6, 18-24, 29-38 of WO 0042174), the narrower scope of transfecting a transgene into a cell, selecting a cell contain transgene, and doing rounds of nuclear transfer to produce first transgenic heterozygous transgenic offspring and second reconstructed embryos and or transgenic offspring that are homozygous and/or heterozygous for the transgene are encompassed by this disclosure. In addition the breadth includes any screening mechanism and characterizations associated with determining the presence of heter/homozygous transgene and molecular biology screening methods such as FISH, Southern blot, PCR as referred to in claim 4 anf a second selective agent of claim 14.

Because nuclear transfer potentially allows for the production of many animal at once and reduces the generation interval as disclosed in WO 0042174 (p. 2 lines 28-29 and p4. lines 22-23), any animal, transgenic or not, will be more quickly developed for any purpose. Therefore, the method of claim 5 wherein homozygous transgenic animal are more quickly developed for xenotransplantation purposes or developed with humanized Ig loci are inherent and disclosed in WO 0042174.

The instant invention claims said donor differentiate, adult or non-adult, quiescent or non-quiescent, mammalian cell be from an ungulate from the group consisting of bovine, ovine, porcine, equine, caprine, and buffalo or rodent (claims 6-10). WO

0042174 discloses that the donor genetic material can be from any differentiated, partially differentiated, non-differentiated cell taken from any stage in animal development such as an embryo, fetus, juvenile, adult animal or any cell line derived from such (p.10 lines 8-11). WO 0042174 also discloses in additional to any animal, ungulate, cow, bull, pig, sheep, goat, camel, waterbuffalo, rodents, lagomorphs, or rabbits in claims 18-23.

WO 0042174 discloses the use of cytocholasin-B to factilitate enucleation (p.7 line 1) as claimed in claim 17 of the instant invention.

WO 0042174 discloses any genetic manipulation for numerous uses including production of human therapeutic proteins in bodily fluids(p.10 lines 18-21). This would encompass any of the biopharmaceutical protein products listed in claim 22 and 23 using a construct containing a beta-casein promoter of claim 24 of the instant invention.

It is emphasized that this 102 rejection is not inconsistent with the 112 1st rejection. Although WO 0042174 descriptively discloses the instant invention, it does not enable the instant invention.

9. Claims 1, 4-11, and 22-24 rejected under 35 U.S.C. 102(e) as being anticipated by US 202/0069423 A1 (f.d. 3/26/2001).

The instant invention is drawn to a method of producing a transgenic animal comprising: transfecting a cell with a construct encoding a desired gene, selecting cells that have integrated the transgene into its genome, performing a first nuclear transfer with cell containing the transgene and producing a heterozygous transgenic animal,

characterizing the genetic composition of said first transgenic animals, selecting cells homozygous for the transgene using a selective agent, characterizing surviving cells, and performing a second nuclear transfer to produce a second homozygous transgenic animal.

US 2002/0069423 A1 discloses the production of a transgenic cow that has a deletion in the PRNP gene. The PRNP knockout cow is produced by transfecting bovine fibroblast cells with a construct containing the PGK promoter with the positive selectable marker, neomycin resistance gene, and the flanking DNA form the PRNP gene (p. 6 [0063] and p. 16 [0165]), selecting cells for ones that have integrated the transgene into their genome by screening with G418 (p. 16 [0167]), expanding surviving cell and screening them using Southern blot analysis (p. 16 [0169]), generating fetus from the surviving transgenic knockout cells and do nuclear transfer to produce transgenic PRNP knockout cows (p. 17 [0170] – p.18 [0204]). The inventor of US2002/0069423 A1 used fetuses to for nuclear transfer but also disclosed that adult animals with transgenic cells can be uses for rounds of nuclear transfer (p. 17 [0172]) as seen in the instant invention. It is also disclosed that homozygous deletions can be selected for using higher concentrations of G418 supplemented in the media (p. 16 [0167]), as similarly described in the specification of the instant application (p. 8 [0025] lines 26-29 and Example 1 lines 10-30). US2002/0069423 further discloses that the method could be used in other cloned transgenic ungulates and mammals (p. 4 [0035]-[0036]) as similarly claimed in the instant invention (claims 6-11). US2002/0069423 also discloses the use of a transgenic construct in the instant application operabley

linked to a milk specific promoter to produce heterologous proteins in the milk (p.4 [0033], as claimed in the instant application (claims 22-24)

It is emphasized that this 102 rejection is not inconsistent with the 112 1st rejection. Although descriptively US2002/0069423 discloses the instant invention, it does not enable the instant invention.

10. Claims 1-11, 14, 17 and 22-24 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,945,577 (Aug 31, 1999).

The instant invention is drawn to a method of producing transgenic animals comprising: transfecting a prescreened cell with a construct encoding a desired gene, selecting cells that have integrated the transgene into its genome, performing a first nuclear transfer with cell containing the transgene and producing a heterozygous transgenic animal, characterizing the genetic composition of said first transgenic animals. Also claimed are the resultant offspring from this method and the resultant milk from the resultant offspring from this method.

US Pat No 5,945,577 discloses several research groups that use ungulate inner cell mass (ICM) cells for nuclear transplantation. Several groups have done nuclear transfer using bovine ICMs as nuclear donor that are microinjected into enucleated mature oocytes. It also discloses culturing embryos in vitro 7 days to produce blastocysts that are transferred into recipient and produce offspring (par bridging col 2 and 3). It further discloses the use of this technology to provide an improved method to

for producing transgenic mammals and a method for multiplying adult mammals having proven genetic superiority or other desirable traits (col 4, line 3-8).

It would be obvious to an artisan that this technique could be repeated in multiple rounds.

11. Claims 1-11, 14, 17, and 22-24 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,633,076 (May 27, 1997).

The instant invention is drawn to a method of producing transgenic animals comprising: transfecting a prescreened cell with a construct encoding a desired gene, selecting cells that have integrated the transgene into its genome, performing a first nuclear transfer with cell containing the transgene and producing a heterozygous transgenic animal, characterizing the genetic composition of said first transgenic animals. Also claimed are the resultant offspring from this method and the resultant milk from the resultant offspring from this method.

US Pat No 5,633,076 discloses that transgenic cows that produce hLF in their milk were produced from bovine morulas developed from microinjected oocytes that were split. One half of the morula is kept in culture to develop into blastocysts while the other half is subjected to DNA analysis prior to transfer of the blastocysts into the recipient. Lactating transgenic offspring were produced that produced h LF in their milk (col 34, lines 54-67).

It would be obvious to an artisan that this could be repeated in multiple rounds.

12. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcia S. Noble whose telephone number is (571) 272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marcia S. Noble

AU1632